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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,103	11/05/2001	A. James Mixson	5627*5	7244

7590

08/25/2004

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EXAMINER

NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
10/018,103	MIXSON, A. JAMES	
Examiner	Art Unit	
Dave T. Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 June 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 and 12-52 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 and 12-52 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2/15/02</u> . | 6) <input type="checkbox"/> Other: _____ |

Claim 11 has been canceled, claims 1-2, 22, 25, 27, 28, 29, 41, 42 have been amended, claims 45-49 have been added by the amendment filed June 1, 2004.

Claims 1-10, 12-49, to which the following grounds of rejection remain and/or are applicable, are pending.

The specification is also objected because this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because page 29, line 14, and page 31, lines 4-6 contain peptide sequence, and oligo sequences, respectively, wherein no SEQ ID NO: is associated with a corresponding disclosed sequence. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) in order to be fully responsive to this office action.

The specification is objected because of typographical errors on page 27, line 2, and page 29, line 31. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-52, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a new matter rejection.

In claim 27, the newly added limitation "linear and having at least 13 amino acids" does not find any written support, which would support specifically for a species of a peptide composed of a linear peptide and having at least 13 amino acids as recited in the claim. Applicant's showing or disclosure of one single 13 amino acid peptide as set forth in SEQ ID NO: 1 is not sufficient for introducing a limitation that cover the breadth of other linear peptides having at least 13 amino acids as presently claimed.

Along the same reasoning as set forth in the immediately preceding paragraph, the limitation "at least about 86% of said amino acid residues of said peptide are selected from the group consisting of non-histidine residues" as recited in claim 29 or claim 42, and the limitation "wherein at least about 27% of the amino acid residues of said peptide are histidine", as recited in the newly added claims 46-51, is also a new matter being introduced into the as-filed application.

In view of applicant's response on pages 13 and 14 of the response dated June 1, 2004, the writtendescription rejection has been withdrawn by the examiner.

However, the following is a new ground of rejection pertaining to the currently claimed subject matter within the context of 35 USC 112, first paragraph.

Claims 1-10, 12-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a negatively charged pharmaceutical agent delivery composition, which comprises of a transport polymer comprising a cationic peptide, characterized as having at least 10 amino acid residues, wherein at least 10% of said amino acid residues are histidine, and wherein the remaining amino acid residues containing in said peptide are non-histidine amino acid(s) with a side group that carries a positive charge at physiological pH,

and a pharmaceutical agent having an overall negative charge.

does not reasonably provide enablement for any other claimed embodiment as presently covered by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

With respect to the currently amended claims, the as-filed specification only teaches and contemplates that an enhanced transport of a pharmaceutical agent having an overall negative charge (for example, nucleic acid) can be achieved by a histidine

containing cationic peptide, which is further characterized as having the remaining non-histidine amino acid residues with a side group that carries a positive charge at physiological pH.

While the specification contemplates generically that the property of enhanced transport of any pharmaceutical agent is the result of the presence of a histidine component in the transport polymeric peptide, regardless of the size of the peptide, regardless of the non-histidine component in the peptide, regardless of whether the peptide is linear or branched, regardless of the peptide concentration, and regardless of the histidine order within the peptide, the specification also teaches and specifically states on pages 13 and 13:

When the pharmaceutical agent has an overall negative charge (for example, nucleic acid) the non-histidine amino acid(s) are preferably selected from the group consisting of amino acid with a side group that carries a positive charge at physiological pH (for example, lysine and arginine). More preferably, the non-histidine amino acid(s) comprise lysine residues. In one aspect of the invention, the non-histidine amino acid(s) are all lysine.

Notwithstanding the above teaching, and particularly on the contrary to applicant's assertion on pages 13 and 14 of the latest response, it is not simply routine to just employ any histidine containing peptide or polypeptide, regardless of all the characteristics as asserted by applicant above, as a transport polymer of any

pharmaceutical agent. For example, Midoux (US Pat No. 6,372,499) teaches on column 3, lines 55-60:

Preliminary results have shown that polyhistidine (very 55
poorly soluble in an aqueous medium at neutral pH) cannot
be used to transfect cells because, since it is not a polycation
at neutral pH, it is not capable of forming with DNA stable
complexes of sufficient solubility to be used at neutral pH,
in particular at pH 7.4, the pH of plasma. 60

The invention relates to new complexes of nucleic acid
and substituted polymer which are capable of transfecting
several types of cells.

The same teaching is disclosed in Midoux, (IDS, Bioconjugate Chem, 10, 3, 406-411, 1999, page 407). As such, and given that a polyhistidine containing linear peptide itself is not found to have any transporting property, it appears to a skilled artisan that in order to transform such polyhistidine containing linear peptide into a transporting polymer, teachings and guidance regarding specifically to the non-histidine residues contained in a histidine containing peptide such as a polyhistidine containing peptide must be disclosed with sufficient details so as to enable the skilled artisan to make and use the claimed peptide as a transporting polymer for a negatively charged agent such as DNA. Such is lacking in the specification so as to cover the entire breadth of the claims. Only embodiments covering essentially of negatively charged molecules/histidine/glycine/lysine containing cationic peptide and liposomal carriers are disclosed with detailed by the as-filed specification and its working examples. Thus, a reasonable skilled artisan would not have reasonably extrapolated from applicant's working examples and positive results, wherein a number of cationic peptides containing both histidine residues and lysine/glycine residues were employed as a transporting cationic polymer in a liposomal complex containing a nucleic acid plasmid

vector, to the entire breadth of the claims as currently pending. In fact, it is not apparent how a skilled artisan, without any undue experimentation, determines as to which order and names of non-histidine amino acids must be specifically arranged in a histidine or polyhistidine containing peptide or polypeptide so as to tailor an intracellular transport of any pharmaceutical agent across the cell membrane. The entire breadth of the claims would cover not just nucleic acid molecules being used as a pharmaceutical agent, but also positive charged drugs, hydrophobic drugs, antibodies, hormones, *etc.* The specification teaches and contemplates that a cell delivery of any pharmaceutical agent can be enhanced with the use of any histidine containing peptide or polypeptide, wherein, for example, only 1 histidine residue is required at minimum for a 10 amino acid peptide, and/or 10% of histidine residues are required for a 150 amino acid or 300 amino acid polypeptide, wherein the rest or remaining amino acid residues can be any non-histidine amino acid residues arranged in an order. Other than a concentrated emphasis on claimed embodiments covering nucleic acid molecules, the as-filed specification does not provide any guidance as to what is necessary or required for the make and use of a histidine containing polypeptide that can be used as a generic transport polymer so as to transport an enormous number of pharmaceutical agents other than negatively charged molecules such as nucleic acid molecules. For example, it is not even apparent how a positive charged cationic peptide containing histidine residues can be used to associate with a positive charged drug and subsequently to enhance the transport of the drug across the cell membrane, particularly since it is well known in the art that cationic peptides are not known to be bound to pharmaceutical

agents having an overall positive charges. Even with a claimed embodiment, wherein a histidine/lysine containing peptide is contemplated as solely transporting peptide for nucleic acid plasmid vector without the help of any other known carriers, such as liposomes, applicant's publication, Chen, Nucleic acid Res, Vol. 30, No. 6, 2002, specifically teaches that "without liposomes the linear HK [histidine/lysine] polymer would have been discounted as a transfection carrier in both endothelial cells and fibroblast". This further bolsters a reasonable conclusion by a skilled artisan of the unpredictable nature of histidine containing peptide or polypeptide being used as a solely cell transporting polymer, particularly on the basis of applicant's disclosure and the prior art of record. While the as-filed specification provide evidential support showing that liposomes in combination with histidine/lysine containing peptides enhanced the expression of reporter genes in transfected cells, such is not claimed specifically in the claims, nor is it representative of the entire breadth of the claims. As such, a skilled artisan would have to engage an undue experimentation to make and use the claimed invention as broadly claimed currently.

Applicant's response (pages 12-15) while obviating the written description rejection is not found persuasive so as to overcome the above enablement rejection.

Applicant's response (pages 15-16) coupled with the 1.131 Declaration by applicant have been considered, and are found persuasive for the withdrawal of the prior art rejection over the PACK reference.

Claims

Art Unit: 1632

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.


DAVE TRONG NGUYEN
Primary Examiner

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632